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Total Synthesis of Cycloaraneosene, a Fundamental Hydrocarbon of "epi"-Fusicoccane Diterpenoids, and the Structure Revision of Its Congener, Hydroxycycloaraneosene

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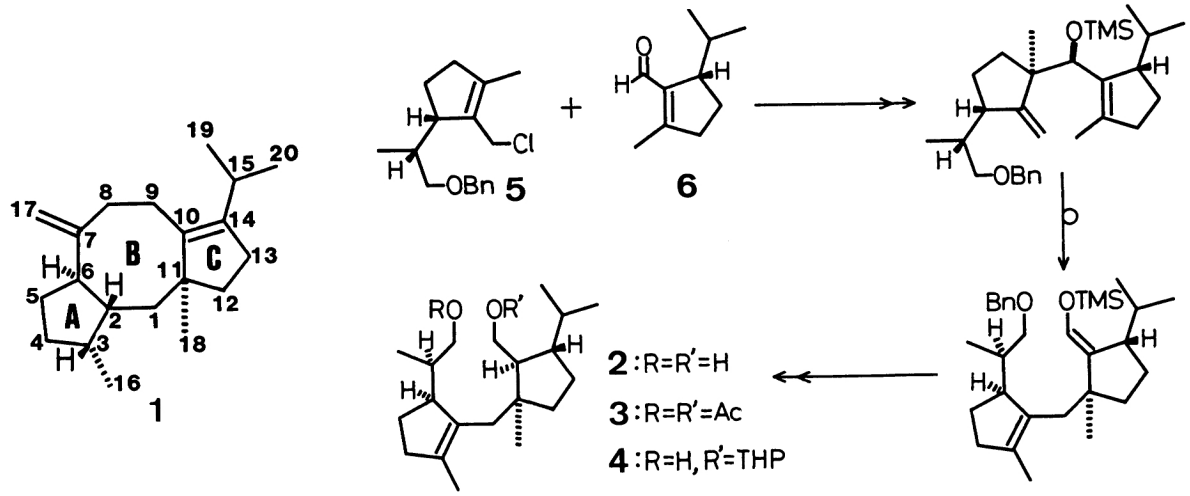
The 5-8-5-membered tricyclic diterpene, cycloaraneosene, has been totally synthesized via the stereoselective condensation of two units of optically active iridoids, Cope rearrangement and chemical reduction of the tetrasubstituted C=C bond. The NMR spectrum of synthetic 9α-hydroxycycloaraneosene was not identical with the congener product, and the natural alcohol is likely to be 8β-hydroxyl derivative.

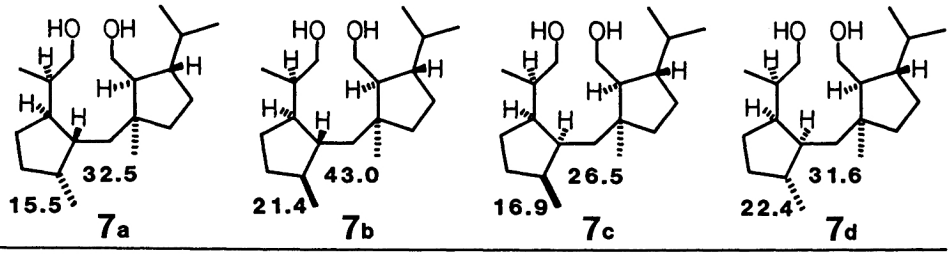
In this paper, we describe the total synthesis of cycloaraneosene (1), a metabolite from Sordaria araneosa Cain[1] and a biogenetic precursor of other oxygenated metabolites. To date, although several workers have reported the related works, no synthesis of the natural products in the family of 5-8-5-membered tricyclic derivatives has been reported.



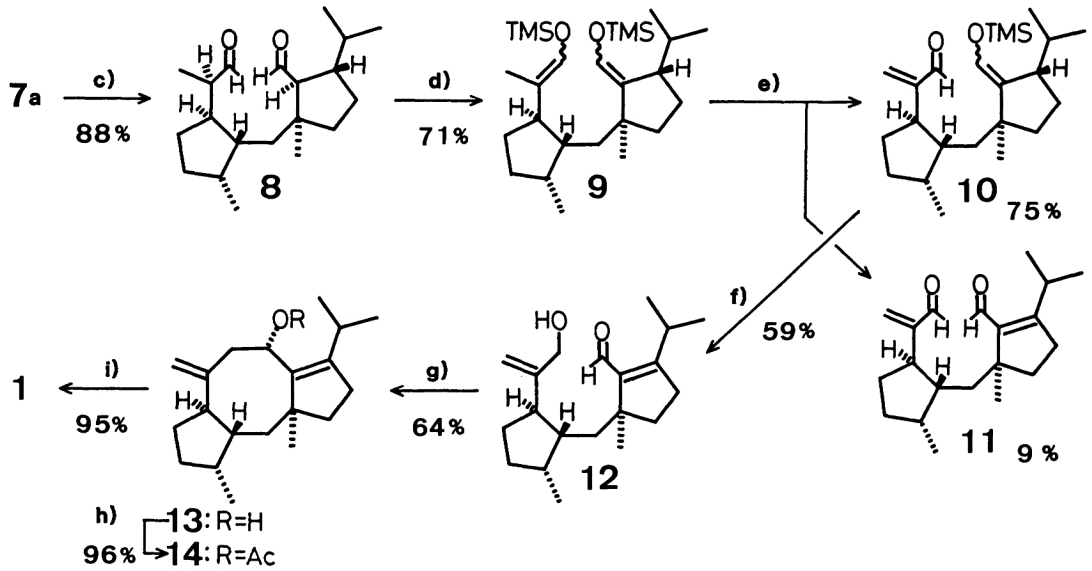
Among the natural 5-8-5-membered tricyclic derivatives, stereochemistry of 1 has two outstanding features: i) syn-relation between C-6-H and C-11-Me is reverse to cotylenins[2] and fusicoccins[3] and ii) C-2-H and C-3-H of the saturated ring A have cis-β-geometry. The former arrangement can be created by the stereospecific Cope rearrangement of a dimeric condensate of appropriate iridoids.[4] Therefore, in order to synthesize 1, the stereoselective reduction of the tetrasubstituted

double bond, which is indispensable for the Cope rearrangement, is crucial.

The key intermediates, the diol (**2**) [^{1}H NMR[5] δ=0.83(3H, d, J=6 Hz), 0.90 (3H, d, J=7 Hz), 0.95(3H, d, J=7 Hz), 1.12(3H, s), 1.61(3H, br s), 3.19(1H, dd, J= 11, 8 Hz), 3.48(1H, dd, J=11, 5.5 Hz), and 3.70(2H, m). ^{13}C NMR δ=15.1, 16.7, 17.8, 22.2, 23.0, 24.5, 28.8, 29.4, 30.8, 36.5, 37.4, 37.7, 46.6, 47.2, 53.2, 56.3, 63.2, 64.4, 135.5, and 135.8] and its derivatives, diacetate (**3**) and monotetrahydropyranyl (THP) ether (**4**), were prepared via the $CrCl_2$-mediated condensation of (3S,8R)-9-benzyloxy-7-chloroirid-1-ene (**5**) and (3S)-irid-1-en-7-al (**6**) and subsequent chemical conversions.[4,6]



3 —a)→	39%	27%	16%	—
4 —b)→	67%	12%	—	3 %



a) H_2/PtO_2/AcOH; $LiAlH_4$/THF, b) Na, ^{t}BuOH/HMPA; p-TsOH/MeOH, c) $(COCl)_2$-DMSO; Et_3N, d) $TMSSO_3CF_3/Et_3N$, e) $Pd(OAc)_2$/MeCN, f) DIBAH/Toluene; $^{1}O_2$(Rosebengal); PPh_3, g) MsCl/Py; $CrCl_3$-1/2$LiAlH_4$/DMF-THF, h) Ac_2O/Py, i) Li, ^{t}BuOH/liq.NH_3.

To generate the correct stereochemistry of A-ring,[7] the hydrogenation must occur from the β-side of **2** or its derivatives. This is likely to be the case since, a molecular model shows that the α-side of A-ring is more blocked than β-side by the substituents on the C-ring. Although every attempt failed to hydrogenate **2**, the PtO_2-hydrogenation of **3** did occur in acetic acid at 70 °C. After hydrolysis, a dihydro diol (**7**a) [^{1}H NMR δ=0.82, 0.84, 0.89, 1.00(each 3H, d,

J=7 Hz), 1.04(3H, s), 3.35(1H, dd, J=10.5, 8 Hz), and 3.5–3.8(3H, m). ^{13}C NMR δ= 15.5, 17.1, 18.1, 22.4, 24.2, 24.9, 27.7, 31.5, 32.5, 33.2, 36.8, 37.4, 38.0, 41.7, 44.9, 47.0, 47.9, 56.1, 64.1, and 65.4] was obtained in 39% yield, together with two by-products, **7**b and **7**c, in 27% and 16% yields, respectively.

The catalytic deuteration of **3** under comparable conditions proved that the major product, **7**a, is the required isomer. Namely, the ^{13}C NMR spectra of corresponding deuterio derivatives showed the complete disappearance of C-2, C-3, and C-16 signals to indicate a rapid hydrogen exchange prior to the reduction. On this ground, no deuterium incorporation at C-6 proved the intactness of configuration at this point. On the basis of the well-known relationship of chemical shift with stereochemistry, the configurations of these products were ascertained; i.e., relatively high field signals for the secondary methyls of **7**a and **7**c suggested that these methyls are cis to the vicinal substituent.[8] By the same argument on the C-1 methylene carbons, relative configurations of C-2 and C-6 of **7**a and **7**c were assigned to be trans and cis. Thus, **7**a is required cis-trans isomer. Remained **7**b, exhibiting both methyl and methylene signals at lower field, must be the trans-trans-isomer.

More selectively, **7**a can be prepared via the following route: **4** was treated with sodium metal and tert-butanol at room temperature in hexamethylphosphoric triamide[9] to afford, after hydrolysis of protecting group, a 22:4:1-mixture of **7**a, **7**b, and the fourth isomer (**7**d) in 82% yield. The absence of **7**c was predictable from the mechanistic view point, and the ^{13}C NMR spectrum of **7**d are reasonable as the trans-cis-isomer on the above mentioned criteria.[10] These figures are found in the illustrations of **7**a–d.

Subsequently, to construct the tricyclic skeleton with proper functionalities for **1**, **7**a was oxidized to dialdehyde (**8**) [^{1}H NMR δ=0.79, 0.80, 0.86, 1.11(each 3H, d, J=7 Hz), 1.17(3H, s), 9.67(1H, d, J=2 Hz), and 9.70(1H, br s)], which was then converted to an isomeric mixture of bis-silylenol ethers (**9**). Upon $Pd(OAc)_2$-treatment,[11] the less hindered enol ether of **9** was preferably oxidized to give **10**; the yield of accompanied dialdehyde (**11**) was only 9%. Diisobutylaluminumhydride reduction and sensitized photooxidation of **10** yielded hydroxyl aldehyde (**12**) [^{1}H NMR δ=0.85, 1.08, 1.09(each 3H, d, J=7 Hz), 1.18(3H, s), 3.39 (1H, sept, J=7 Hz), 3.97(2H, br s), 4.81(1H, br s), 5.06(1H, m), and 9.91(1H, s)]. Consecutive treatment of **12** with methanesulfonyl chloride and $CrCl_2$[12] gave a single cyclisate (**13**) [^{1}H NMR δ=0.84, 0.91, 0.96(each 3H, d, J=7 Hz), 1.20(3H, s), 2.73(1H, sept, J=7 Hz), 4.77(1H, dd, J=8, 7 Hz), 4.79(1H, br s), and 4.95(1H, br s). ^{13}C NMR δ=17.6, 21.5, 21.9, 27.1, 27.9, 28.6, 29.8, 31.4, 38.2, 38.7, 40.7, 41.0, 45.1, 50.4, 51.5, 69.1, 113.5, 139.3, 148.2, and 148.7]. The chemical shift of the singlet methyl, δ=1.20, indicated the syn-relationship with the allylic hydroxyl group.

The final transformation was achieved through a reductive elimination of the allyl alcohol via the acetate (**14**). Compound **1** thus obtained was identical with natural (-)-cycloaraneosene in all respects, including the optical rotation.[13]

Incidentally, the structure of **13** is same to that proposed for a congener metabolite, hydroxycycloaraneosene (**13A**).[1] However, the physical data of **13** was clearly different from those recorded for the natural product or its epimer

derived by chemical transformations.[1] Thus, **13**, colorless scales, mp 64–65 °C, revealed a negative rotation ($[\alpha]_D$ -21.8°), On the other hand, **13A**, a colorless oil, was positive ($[\alpha]_D$ +7.5°). In the ^{1}H NMR spectrum, the singlet methyl of **13A** was at δ=1.02. Presumably, **13A** is 8β-hydroxy derivative of **1**.

Synthesis of other members of terpenoids via this strategy is currently in progress.[14]

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5) The NMR spectra were measured by a JEOL FX 100 Spectrometer in $CDCl_3$ solution, and the chemical shifts expressed were in δ unit.
6) Details of these transformations should be described in a full paper. All new compounds described here have been fully characterized.
7) The positional numbers and ring letters shown in **1** are used throughout in this paper.
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13) Among all physical data of **1** showing a good agreement, the specific rotation, $[\alpha]_D$ -37.5° (lit[1] -38.4°), and the ^{13}C NMR (values in parentheses are deviated magnitudes from the reported values) [δ=16.4(+0.1), 21.2(-0.1), 21.3, 24.2(+0.1), 26.9, 27.1, 27.4, 31.7(-0.1), 33.1, 35.9, 36.0(-0.1), 39.2, 40.5, 47.2(-0.1), 49.3(+0.1), 50.8(+0.1), 110.6(-0.1), 138.9, 142.4(-0.1), and 156.0 (-0.1)] should be sensitive to the stereostructure.
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